Paper

DOSE RESPONSE AND TEMPORAL PATTERNS OF RADIATION-ASSOCIATED SOLID CANCER RISKS

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Abstract—**Findings of the Life Span Study (LSS) cohort of atomic-bomb survivors are a primary source for quantitative risk estimates that underlie radiation protection. Because of the size and length of follow-up, the LSS provides considerable information on both the nature of the dose response and on how radiation-associated excess risks vary with age, age at exposure, sex, and other factors. Our current analyses extend the mortality follow-up by 7 y (through 1997) and add 8 y (through 1995) to the incidence follow-up. During the follow-up periods there have been a total of about 9,300 solid cancer deaths and almost 12,200 incident cases. As outlined in this presentation, while discussing issues related to the shape of the dose response and low dose risks in some detail, the new reports consider temporal patterns in greater detail than has been done previously. As we have reported, the LSS solid cancer dose response is well described by simple linear dose response over the 0 to 2 Sv range (with some leveling off at higher estimated doses). This remains the case with the extended follow-up. Although LSS is often referred to as a high dose study, about 75% of the 50,000 cohort members with doses in excess of 5 mSv have dose estimates in a range of direct interest for radiation protection (0–200 mSv). Analyses of data limited to this low dose range provide direct evidence of a significant solid cancer dose response with a risk per unit dose that is consistent with that seen for the full dose range. Previous LSS reports have focused on descriptions of the solid cancer excess risks in which the excess relative risk varies with age at exposure and sex. In addition to the age at exposure effects, our current analyses suggest excess relative risks also vary with age (at death or diagnosis). Excess relative risks are higher for those exposed earlier in life, with attained age-specific risks changing by about 20% per decade, but tend to decrease with increasing attained age, roughly in proportion to (1/attained-age)$^{1.5}$, for any age at exposure. Despite the decreasing relative risk, excess rates have increased rapidly throughout the study period with some indication, especially for the incidence data, that attained-age-specific rates are higher for those exposed at younger ages. Simple comparisons of site-specific excess risks are used to illustrate how the interpretation of age-at-exposure effects on excess relative risks or excess rates is complicated by changes in baseline rates with birth cohort or time period.**

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INTRODUCTION

The Life Span Study (LSS) cohort of atomic bomb survivors is providing increasingly detailed information on the nature of radiation-associated cancer risks. LSS findings (Pierce et al. 1996; Shimizu et al. 1999) are a primary source for the quantitative risk estimates that underlie radiation protection (NAS/NRC 1990; ICRP 1991; UNSCEAR 2000a, 200b). However, it is becoming more apparent that risk estimation cannot be separated from understanding of the age patterns of the excess risk. There is also growing recognition of the LSS as an important source of information on the biological mechanisms associated with radiation effects on cancer (and noncancer) disease incidence. We are currently completing a new series of analyses that extend by 7 y the previously reported mortality follow-up (through 1997) and add 8 y to the incidence follow-up (through 1995). During these follow-up periods there have been a total of about 9,300 solid cancer deaths and almost 12,200 incident cases. We estimate that about 5% of the solid cancer deaths and 6% of the incident cancers are attributable to the atomic bomb radiation exposure. In this presentation we touch upon some of the issues that will be considered in the new reports, including low dose risks, the shape of the dose response, and descriptions of and generalizations about temporal patterns in radiation-associated excess risks. We conclude with brief comments on the interpretation of site-specific differences in the pattern of the excess risks and the difficulties in making useful inferences about the effect of interactions between radiation and other (genetic or environmental) risk factors from the LSS data.

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LOW DOSE EFFECTS AND THE SHAPE OF THE DOSE RESPONSE

The LSS cohort is often mischaracterized as a high dose study. In fact, about 75% of the 50,000 cohort members with doses in excess of 5 mSv received doses of less than 200 mSv. As we have recently reported (Pierce and Preston 2000), useful risk estimates can be derived from analyses of the data for survivors over this relatively low-dose range. The excess risks for both cancer incidence and mortality are well-described by a simple linear dose response over this range, and the trend with dose is statistically significant over an even more restricted dose range. The estimated risk per unit dose over this low dose range is quite consistent with that obtained in analyses of cohort members with dose estimates in the 0–2 Sv range. There is no indication of a threshold in the LSS dose response. For both the mortality and the incidence data the best estimate of the threshold is zero and the upper 90% confidence limit on the threshold is between 60 and 100 mSv. The dose response begins to level off around 2 Sv reflecting the impact of uncertainties in individual dose estimates and possible impact of cell-killing at higher doses.

While our results demonstrate that the LSS can provide useful characterizations of cancer risks associated with acute low-dose exposures, there are of course limitations related to the usual difficulties of epidemiological studies. The LSS data suggest that solid-cancer mortality lifetime risks at doses of interest for radiation protection (say 50–100 mSv) are likely to be increased by about 1–2%. However, even in a large well-defined cohort drawn from a generally homogenous population, mortality or incidence rates among the subsets of the zero dose (unexposed) group can easily exhibit variability (or bias), comparable to the low dose effect, for reasons that are unrelated to exposure (Cologne and Preston 2000, 2001). However, this problem is less severe in the LSS than in most epidemiological studies because of the steep gradient of dose with distance (all survivors with doses in excess of 5 mSv were within 2.8 km of the hypocenter), the large size of the cohort, and the availability of adequate individual dose estimates.

AGE- AND AGE-AT-EXPOSURE EFFECTS ON RADIATION-ASSOCIATED CANCER RISKS

Previous LSS reports, and risk estimates developed on the basis of these reports, have generally focused on descriptions of solid cancer excess risks in which the excess relative risk (ERR) is constant in attained age but varies with age at exposure and sex. In the current analyses we are finding increasingly compelling evidence that ERRs also decrease with increasing attained age. The ERR decreases with attained age roughly in proportion to $(1/\text{attained-age})^{1.5}$, for any age at exposure, while the age at exposure effect can be described by a 20% decrease in attained-age-specific ERRs per decade increase in age at exposure. However, as discussed below, interpretation of this age-at-exposure effect is complicated by birth cohort effects (or secular trends) in background rates. Despite the decrease in the relative risk with increasing attained age, excess absolute rates (EAR) have increased rapidly throughout the study period regardless of the age at exposure. There are indications that for all solid cancers as a group attained-age-specific EARs, like the ERRs, tend to be higher for those exposed at younger ages.

Since the relative risk does not appear to be constant in time, even within age at exposure groups, it is not possible to summarize "the" risk associated with a given exposure by a single ERR value. Thus, simple summaries over attained age, such as lifetime risk estimates together with measures of lost lifetime, are increasingly important descriptions of radiation effects. Lifetime risk, as defined in UNSCEAR (2000b), is the sum over attained ages of the difference in rates for an exposed and an unexposed population (which is otherwise identical) weighted by survival probabilities for each age. This means that lifetime risk estimates account for both the risk of developing a radiation-associated disease that would not otherwise have occurred and the risk of developing the disease earlier than would have occurred without exposure.

SITE-SPECIFIC RISK ESTIMATES

While risk estimates for all solid cancers as a group provide useful and important summaries of radiation effects on cancer risks, consideration of site-specific risk estimates is important both for radiation protection and for developing a better understanding of how radiation affects cancer mortality or incidence rates. However, because of the limited number of radiation-associated cases for any specific type of cancer, inferences about the existence of radiation effects or the temporal pattern of the excess risks for specific sites are imprecise.

At the simplest level, specific tumor types are often classified as "radiogenic" (rates are increased by radiation exposure) or "nonradiogenic" (rates are unaffected by radiation exposure) depending on whether or not the null hypothesis of no dose effect can be rejected in a simple analysis of site-specific rates. However, in view of the clear evidence for radiation effects on solid cancer incidence, this approach is misleading. The failure to detect a significant radiation dose response in a site-specific analysis is at least as likely to reflect a lack of

power due to the small expected number of radiation-associated events as it is to indicate the actual absence of a dose response.

Prostate cancer, which the most recent UNSCEAR (2000a, 2000b) report singles out as an example of a cancer for which there is no indication of an association with radiation, can be used to illustrate this problem. Using the LSS cancer incidence data, we cannot reject the null hypothesis that there is no radiation effect on prostate cancer ($p = 0.3$). However, the estimated ERR per sievert (0.3 based on 243 cases) is quite similar to the male solid cancer ERR estimate (0.35, based on about 5,400 cases), suggesting that one cannot conclude from the LSS data that there is no evidence of radiation effects on prostate cancer risks. Generally speaking, as we have indicated in Pierce et al. (1996), the observed variability in site-specific estimates of the solid cancer ERR per sievert is comparable to that expected under a hypothesis that there is a common ERR for all solid cancer types. Therefore, real, but relatively small, variations in site-specific ERRs are difficult to assess.

Comparison of age-time patterns in the excess risks for specific types of cancers is another area of interest. Particular cancers for which the temporal pattern of the excess risks differs markedly from those for solid cancers as a group may be promising candidates for molecular epidemiological analyses. However, even more than for the dose response, it is difficult to interpret age-time patterns (particularly age at exposure effects) and to identify sites with unusual temporal patterns. There are two primary reasons for this. The first is, as noted for dose response differences, a lack of power due to the small number of radiation-associated cancers. The second is related to the fact that age-time patterns, particularly age-at-exposure effects, strongly depend on the nature of secular trends in background rates. For example, in contrast to solid cancers as a group where attained-age-specific ERRs tend to decrease with increasing age at exposure, the attained-age-specific incidence ERR estimates for lung cancer incidence in the LSS are higher for survivors who were older at the time of the bombings while excess rates exhibit almost no age at exposure effect. The primary reason for this unusual pattern is the marked increase in smoking for cohort members who were younger at the time of exposure. Such factors affect both the interpretation of and how to generalize LSS cancer risks estimates.

INTERACTIONS

There is increasing interest in using the LSS data to investigate possible interactions between radiation and environmental or genetic risk factors. The LSS is particularly attractive for such investigations because it is a well-characterized cohort with a broad range of well-estimated radiation doses drawn from a homogenous population with comprehensive long-term mortality and cancer incidence follow-up for all cohort members and supplementary epidemiological (mail survey), clinical, and histopathological data for many members. Indeed, the LSS can be an excellent population for studies of the direct effects of risk factors other than radiation on disease risk, as evidenced for example by recent work on dietary risk factors and cancer in this cohort (Nagano et al. 2000, 2001).

However, the power to detect gene-radiation or radiation-environment interactions is limited by the small number of cancer cases among people with high radiation doses and significant "exposure" to the other risk factor. At present there are 50–200 cases of each of the most common types of cancer among the 5,400 LSS cohort members with doses in excess of 0.5 Sv. (The number of cases will double over the next 20–30 y.) Risk estimates suggest that about one-third of these cases are radiation-related. The number of cases useful in risk-factor interaction studies is further limited by the availability of data on nonradiation risk factors (e.g., data on smoking is available for about 70% of lung cancer cases while the fraction of cases with information on other factors, including genetic markers, will generally be less than this). With such small numbers of cases it is, and will continue to be, difficult to make precise inferences about risk factor interactions. Despite the lack of power to detect or precisely quantify risk-factor interactions in the LSS, carefully planned and thoughtfully interpreted studies can be useful in the characterization of relatively large interactions (e.g., additive vs. multiplicative joint effects of smoking and radiation on lung cancer rates).

CONCLUSION

The LSS is, and will continue to be, the primary source for quantitative estimates of the risk of acute radiation exposures. In addition, because of the availability of biological materials (including serum and whole blood samples and accessible autopsy and biopsy tissue specimens) and comprehensive clinical and laboratory data for a large number of cohort members, the LSS will become an increasingly important population for application of the "new (genome-based) biology." However, in order to take full advantage of the strengths and understand the limitations of these data, epidemiologists, biologists, and statisticians must work together to develop a clear understanding of how best to obtain and analyze data on and interpret the findings from the LSS

cohort. The LSS has proven to be an extremely valuable source of information on the long-term effects of radiation. With effective planning and management and careful analyses, the cohort can become an even more important source of information on cancer risks from radiation and other risk factors and for understanding the mechanisms of carcinogenesis.

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